In This Issue

Cell

Ricin Stopped at the Golgi Border

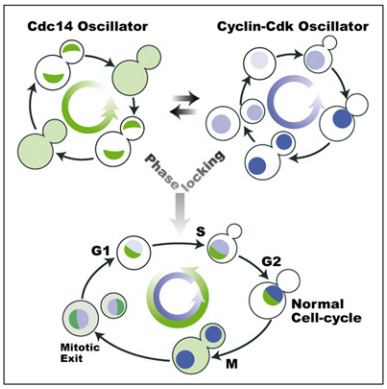
PAGE 231

To gain access to cellular targets, many toxins follow a retrograde transport route from endosomes to the endoplasmic reticulum via the Golgi apparatus. Now, Stechmann et al. use high-throughput screening to identify small molecules that protect mammalian cells against the plant ricin toxin and bacterial Shiga-like toxin. These molecules were highly selective for blocking toxin traffic at the endosome-Golgi interface without affecting compartment morphology or other trafficking steps. One compound protected mice from lethal nasal exposure to ricin.

Synchronizing Cycles within Cycles

PAGE 268

Oscillations in cyclin-dependent kinase (Cdk) activity are believed to control the yeast cell cycle by triggering key events, such as the release of Cdc14 phosphatase from the nucleolus to drive mitotic exit. Lu and Cross now find that Cdc14 release cycles are present even when Cdk is constitutively active. Moreover, cyclin concentration controls the frequency of Cdc14's cycles, suggesting that cyclin-Cdk oscillations lock Cdc14 release at once-per-cell-cycle through entrainment or a ''phase-locking'' mechanism.



Brca1 Mutations: Two Wrongs Make It Better

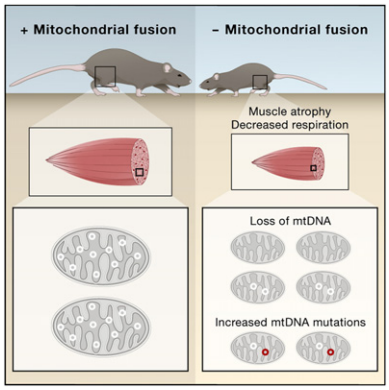
PAGE 243

Mutations in the Brca1 gene lead to genomic instability and predispose carriers to breast and ovarian cancer. Brca1 is thought to suppress malignancy by promoting homologous recombination (HR). Now, Bunting et al. show that the 53BP1 protein inhibits HR in Brca1-deficient cells by promoting a mutagenic DNA repair pathway, called nonhomologous end joining. Importantly, inactivation of 53BP1 restored HR and reduced tumorigenesis in Brca1-deficient cells by increasing resection of broken DNA ends, a key step in HR.

No Gap Left Behind

PAGE 255

Damaged DNA poses a serious problem for DNA replication, potentially leading to genome instability and cancer. To cope with this problem, eukaryotes evolved the *RAD6* DNA damage tolerance pathway, which is believed to operate directly at the replication fork. Now, Karras and Jentsch show that the *RAD6* pathway can function effectively even when uncoupled from the replication fork and after the completion of chromosomal replication. Their findings suggest that the *RAD6* pathway operates on single-stranded gaps left behind the moving replication fork.



A Kiss of Life for Mitochondria

PAGE 280

Mitochondria are dynamic organelles that continually fuse together, but the physiological purpose of this fusion is poorly understood. Here, Chen et al. demonstrate that mice lacking the mitochondrial fusion proteins Mfn1 and Mfn2 in skeletal muscle develop severe myopathy associated with mitochondrial DNA (mtDNA) instability. Moreover, loss of Mfn1 greatly aggravates mitochondrial dysfunction and lethality in mice with already elevated levels of mtDNA mutations. Thus, mitochondrial fusion may protect cells from high levels of mtDNA damage by preserving and replenishing mitochondrial function.

Feeding the Ragulator

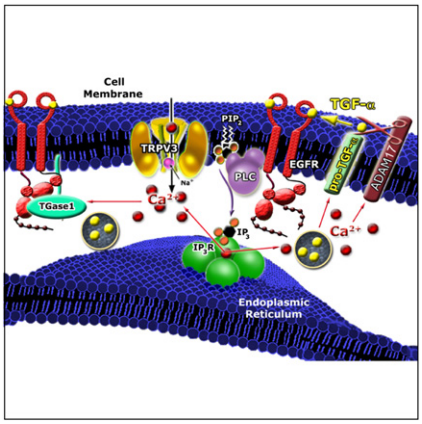
PAGE 290

The mTORC1 kinase, whose activity is often deregulated in cancer and diabetes, promotes cell growth in response to energy levels and amino acid availability. Sancak et al. now show that amino acids cause mTORC1 to move to the surface of the lysosome, where its activator Rheb resides. This translocation depends on Rag GTPases and a trimeric "Ragulator" complex, which tethers the GTPases to the lysosomal surface. These findings demonstrate a previously unappreciated role of lysosomes in mTORC1-mediated amino acid sensing.

Channels Condition Curls

PAGE 280

Growth factors, such as TGF-α, regulate keratinocyte proliferation and differentiation that control hair morphogenesis. Now, Chen et al. find that mice lacking the TRP channel gene *TRPV3* surprisingly display the same curly-hair phenotype as mice with mutations in TGF-α or the epidermal growth factor receptor (EGFR). The authors show that EGFR activation increases TRPV3 channel activity, which in turn stimulates TGF-α release. In addition, TRPV3 forms a complex with EGFR, demonstrating that a TRP channel can directly regulate signaling.



Dynein en-LIS-ts Help for Heavy Loads

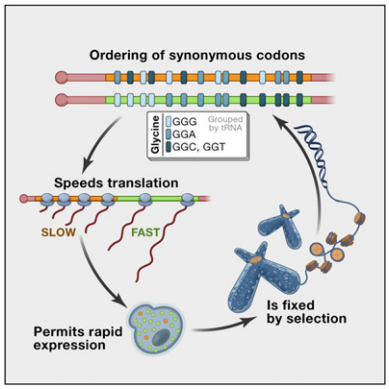
PAGE 304

LIS1 and NudE, which are both linked to neurodevelopmental diseases, regulate intracellular transport by dynein motor proteins. Using single-molecule approaches, McKenney et al. now uncover the mechanism of LIS1 and NudE function. They find that the proteins associate with dynein, stabilize its interactions with cargo, and enable multiple dynein complexes to work synergistically while transporting high loads, such as chromosomes and nuclei. These findings provide insights into how transport defects link to neuronal pathologies.

The Free Chains that Bind RIG-I

PAGE 315

The host cell protein RIG-I binds to invading viral RNA and triggers a signaling cascade that culminates in the production of type-I interferons and other antiviral molecules. By reconstituting the full RIG-I pathway in vitro, Zeng et al. now demonstrate that RIG-I activation requires not only viral RNA but also a unique form of host polyubiquitin chains not attached to any cellular target. These "unanchored" polyubiquitin chains potently activate RIG-I and thus, represent a new class of intracellular signaling molecules.



mRNA Sets Ribosomal Speed Limits

PAGE 344 and PAGE 355

Cells control the efficiency of translation with various protein regulatory factors. Using computational approaches, both Tuller et al. and Cannarozzi et al. now find that translational efficiency is also hardwired into the transcript sequence. Tuller et al. show that messages often start with codons that correspond to rare transfer RNAs (tRNAs). This forms an early elongation "ramp" that fosters slow translation and may maximize the efficiency of protein production. Cannarozzi et al. find that once a codon for a particular amino acid is used, the subsequent codons for that amino acid are likely to be the same, despite the availability of multiple codons for each amino acid. This correlation is highly conserved across organisms and is shown to increase translation speed, suggesting that tRNAs are recycled and channeled by the ribosome.